UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/458,978	06/02/95	EDELMAN E	M116584

18M2/0116

PATREA L PABST
ARNALL GOLDEN & GREGORY
2800 ONE ATLANTIC CENTER
1201 W PEACHTREE STREET
ATLANTA GA 30309-3450

EXAMINER	
NAFF, D	
ART UNIT	**PAPER NUMBER**
1808	4

DATE MAILED: 01/16/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☒ Substitute PTO-948.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-19 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-19 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claims examined on the merits are 1-19 which are all claims in the case.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In line 7 of claim 1, the meaning and scope of "site near to" is uncertain. Being near to is relative and subjective. Additionally, in line 7, there is not antecedent basis for blockage as an alternative to injury. The claim preamble mentions only injury. Moreover, it appears blockage could be considered an injury.

Bridging lines 1 and 2 of claim 1, and where recited in other claims "inhibiting smooth muscle cell proliferation or restenosis of a blood vessel" is confusing since it is unclear as to how these two alternatives differ. It appears inhibiting restenosis involves inhibiting smooth muscle cells or the converse. To be clear, alternatives must be mutually exclusive. It is suggested that one or the other be deleted.

Alternatives that are not mutually exclusive also occur in other claims. In claims 3 and 13, a gel can be a foam or the converse. In claims 6 and 16, carbohydrates are polysaccharides or the converse. In claims 8 and 18, any of the members of the Markush group could be an anti-inflammatory agent. In regard to angiotensin, requiring related compounds is confusing since it is uncertain as to characteristics a compound must have to be related. Other members of the group could be immunosuppressants, and vitamins and free radical scavengers could be

anti-oxidants. Also, other members could be angiogenic and angiogenic inhibitory factors. In claim 14, any of the cells of the group could be "genetically engineered cells".

In claim 12, the meaning and scope of "peripheral bypass surgery" and "organ transplantation" are uncertain. How does peripheral bypass differ from coronary bypass, and what parts of the body are an organ and not an organ? There does not appear to be a sharp line of demarcation between these alternatives.

In claim 19, a surface that is modified to alter cell-matrix interactions is uncertain since the claim does not specify a difference in cell-matrix interaction that is altered interaction.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6, 10-16 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Yannas ('900).

The claims are drawn to a method and composition for inhibiting smooth muscle cell proliferation at an injury to vascular tissue with a polymeric matrix seeded with endothelial cells that is implanted near to or at the injury.

Yannas discloses a blood vessel prosthesis. The prosthesis is a multilayer tubular structure having a nonporous inner polymeric layer and a porous polymeric outer layer (col 2, lines 54-68). The inner and

outer layers may be made of collagen-aminopolysaccharide (col 5, lines 14-16, and col 6, lines 50-55). The inner layer may be seeded with endothelial cells (col 2, line 62; col 7, line 32; and col 10, line 15). The prosthesis can be used as a patch graft for a blood vessel wall (col 7, line 49)

When the blood vessel prosthesis of Yannas contains endothelial cells and is used as a patch graft for a blood vessel wall, smooth muscle cells proliferation is inherently inhibited.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yannas ('900).

The claim requires the endothelial cells to be obtained from biopsy of a patient.

Yannas is described above.

It would have been a matter of obvious choice to obtain the endothelial cells seeded by Yannas from biopsy of a patient since obtaining cells in this way is highly conventional.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yannas in view of Vacanti et al ('612).

The claim requires culturing the endothelial cells *in vitro* prior to implanting *in vivo*.

Yannas is described above.

Vacanti et al disclose seeding a polymeric matrix with cells and implanting to replace tissue. The matrix may contain angiogenic and other bioactive compounds in addition to the cells (col 5, lines 5-10 and lines 24-30). The cells are cultured *in vitro* in the matrix prior to implanting until adequate cell volume and density has developed for cells to survive and proliferate *in vivo* (col 3, lines 22-25).

It would have been obvious to culture *in vitro* the endothelial cells in the blood vessel prosthesis of Yannas to obtain adequate cell volume and density for implanting as taught by Vacanti et al.

Claims 7, 8, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yannas ('900) in view of Edelman et al ('828) or ('039) or ('532) taken with Vacanti et al ('612).

The claims require the matrix to be made of a specific polymer such as ethylene vinyl acetate and the matrix to contain a biologically active compound such as angiotensin or an angiogenic factor.

Yannas is described above.

Edelman et al ('928) disclose (paragraph bridging cols 2 and 3) administering a modulator of cell growth such as angiotensin or an angiogenic factor that affects angiogenesis, smooth muscle cell proliferation or vascularization (col 3, lines 12-25) to the outside of a tubular structure such as a blood vessel for the purpose of regulating cell growth for repair of the blood vessel following injury. The modulator is delivered to the site in a polymeric matrix such as made from ethylene-vinyl acetate (col 3, lines 26-50). The matrix containing the modulator is placed at an extraluminal site adjacent an injured lumen such as an artery (col 4, lines 28-25).

Edelman et al ('039) and ('532) disclose similar to Edelman et al ('928).

Vacanti et al is described above.

It would been obvious to include with the endothelial cells in the blood vessel prothesis of Yannas a modular such as an angiogenic factor as taught by Edelman et al to obtain its affect of controlling smooth muscle cell proliferation since it would have been apparent from Vacanti et al (col 5, lines 5-11) that an angiogenic compound can be incorporated in a matrix containing seeded cells for implanting to generate and repair tissue *in vivo*. It would have been further obvious to substitute for the multilayer prosthesis of Yannas a matrix made

from ethylene-vinyl acetate as taught by Edelman et al since this matrix would been expected function well with the modulator and be capable of functioning as a patch graft for a blood vessel wall.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edelman et al ('928) or ('039) or ('532) in view of prior art disclosed in the specification (under "Background of the Invention" beginning on page 1) and Yannas ('900) and Vacanti et al ('612), and if necessary in further view of Barrera et al ('665) or Yannas et al ('691).

The invention is described above.

The references are described above except for the prior art described in the specification, Barrera et al and Yannas et al .

The specification discloses that it is known that endothelial cells produce compounds that inhibit undesirable proliferation of smooth muscle cells in blood vessels after injury or lesion that causes removal of endothelial cells (paragraph bridging pages 2 and 3).

Barrera et al disclose seeding cells into a polymeric matrix and implanting to generate and repair tissue *in vivo*. Various cells can be seeded depending on the kind of tissue produced *in vivo*, and the cells can be uroendothelial cells (col 11, lines 20-26).

Yannas et al disclose seeding cells into a fibrous lattice and implanting to generate and repair tissue *in vivo*. The cells seeded can be endothelial cells (col 7, line 4).

It would have been obvious to incorporate endothelial cells in combination with the modulator such as an angiogenic factor in the

polymer matrix of Edelman et al for repairing injured blood vessels to replace endothelial cells removed by injury to obtain the function of the cells that is known in the prior art as disclosed in the specification, i.e. the function to produce inhibitors of smooth muscle cell proliferation that results from endothelial cell removal by blood vessel injury. The disclosure by Yannas of incorporating endothelial cells in a blood vessel prothesis to generate endothelial cells for blood vessel repair *in vivo* and by Vacanti et al (col 5, lines 5-10) of incorporating both cells and an angiogenic compound in a matrix for implanting to generate and repair tissue *in vivo* would have suggested that endothelial cells will function in combination with the modulator in the matrix of Edelman et al to replace endothelial cells removed from a blood vessel by injury. The disclosures of Barrera et al and Yannas et al of also implanting matrices containing endothelial cells to generate and repair tissue, if needed, would have further suggested providing endothelial cells in the matrix of Edelman et al to replace endothelial cells removed by injury to a blood vessel.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, claims 1-10 or claims 1-24 of U.S. Patent No. 5,540,928, 5,455,039 or 5,527,532, respectively, in view of prior art disclosed in the specification (under "Background of the Invention" beginning on page 1) and Yannas ('900) and Vacanti et al ('612), and if necessary in further view of Barrera et al ('665) or Yannas et al ('691) for the type of reasons set forth in the rejection under 103 supra over the references.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

The fax phone number is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DMN
1/9/97

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1808